Association of Markers of Microvascular Dysfunction With Prevalent and Incident Depressive Symptoms

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The Maastricht Study

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Abstract—The etiology of late-life depression (LLD) is still poorly understood. Microvascular dysfunction (MVD) has been suggested to play a role in the etiology of LLD, but direct evidence of this association is scarce. The aim of this study was to investigate whether direct and indirect markers of early microvascular dysfunction are associated with prevalent and incident LLD in the population-based Maastricht Study cohort. We measured microvascular dysfunction at baseline by use of flicker light-induced retinal vessel dilation response (Dynamic Vessel Analyzer), heat-induced skin hyperemic response (laser- Doppler flowmetry), and plasma markers of endothelial dysfunction (endothelial dysfunction; sICAM-1 [soluble intercellular adhesion molecule-1], sVCAM-1 [soluble vascular adhesion molecule-1], sE-selectin [soluble E-selectin], and vWF [Von Willebrand Factor]). Depressive symptoms were assessed with the 9-item Patient Health Questionnaire (PHQ-9) at baseline and annually over 4 years of follow-up (n=3029; mean age 59.6±8.2 years, 49.5% were women, n=132 and n=251 with prevalent and incident depressive symptoms [PHQ-9≥10]). We used logistic, negative binominal and Cox regression analyses, and adjusted for demographic, cardiovascular, and lifestyle factors. Retinal venular dilatation and plasma markers of endothelial dysfunction were associated with the more prevalent depressive symptoms after full adjustment (PHQ-9 score, RR, 1.05 [1.00–1.11] and RR 1.06 [1.01–1.11], respectively). Retinal venular dilatation was also associated with prevalent depressive symptoms (PHQ-9≥10; odds ratio, 1.42 [1.09–1.84]), after full adjustment. Retinal arteriolar dilatation and plasma markers of endothelial dysfunction were associated with incident depressive symptoms (PHQ-9≥10; HR, 1.23 [1.04–1.46] and HR, 1.19 [1.05–1.35]), after full adjustment. These findings support the concept that microvascular dysfunction in the retina, and plasma markers of endothelial dysfunction is involved in the etiology of LLD and might help in finding additional targets for the prevention and treatment of LLD. (***Hypertension*. 2020;76:342-349. DOI: 10.1161/HYPERTENSIONAHA.120.15260.)** ● **Data Supplement**

Key Words: cohort studies ■ depression ■ dilatation ■ epidemiology ■ hyperemia ■ microcirculation

Late-life depression (LLD) is a complex mood disorder with high comorbidity of psychiatric and physical diseases and cognitive decline.[1–3] Incidence rates of LLD vary from 0.2 to 14.1/100 person-years.[4] LLD has been associated with increased mortality,[5] and its pathophysiology is complex and still poorly understood.[6] Over half of older adults with LLD fail to remit with first line antidepressant medication.[7] It has been suggested that individuals with treatment-resistant LLD might suffer from a vascular subtype of depression and therefore may not benefit from the current standard care.[8] In light of the increasing elderly population,[9] incidence of LLD will increase. Therefore, it is imperative to gain a better understanding of its etiology.

Increasing evidence suggests that cerebral microvascular dysfunction (MVD) may contribute to the onset of LLD by inducing chronic ischemia in brain tissue.[10] Chronic ischemia results from structural or functional occlusion that may result in cognitive and behavioral problems.[10] When regions of the brain that are involved in mood regulation are affected, this may contribute to the development of depression.[11] Indeed, our recent meta-analysis[12] showed associations of MRI markers of cerebral small vessel disease (CSVD) with incident depression.

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Although it has been shown that structural damage in the brain may already start at middle age,[13] most studies related to LLD only included participants >65 years of age when widespread cerebrovascular changes exist. MRI markers of CSVD may reflect structural consequences of long-term MVD, which are themselves preceded by functional changes.[14] MVD can be measured noninvasively in various organs. Direct measures include flicker light–induced retinal arteriolar and venular dilation response and heat-induced skin hyperemia.[15] Indirect markers of MVD include plasma biomarkers of endothelial dysfunction (ED).[16] CSVD is closely linked to brain microvasculature structure, and evidence indicates that CSVD originate from cerebral MVD.[14,17] Retinal arteriolar and venular dilation response are also closely linked to the brain microvasculature.[18] In addition, to the extent that MVD is a generalized phenomenon, plasma biomarkers of ED and skin hyperemia may also reflect brain MVD.[19]

No previous studies have investigated the association between direct markers of MVD with prevalent and incident depressive symptoms. Therefore, the aim of this study was to determine, in a population-based setting of individuals aged between the 40 and 75 years old, whether markers of MVD as measured in retina, skin, and plasma are associated with prevalent and incident depressive symptoms, independently of demographic, cardiovascular, and lifestyle risk factors.

Methods

Data Availability

The data of this study derive from The Maastricht Study, but restrictions apply to the availability of these data, which were used under license for the current study. Data are however available from the authors upon reasonable request and with permission of The Maastricht Study management team.

Study Population and Design

We used data from The Maastricht Study, an observational population-based cohort study. The rationale and methodology have been described previously.[20] In brief, the study focuses on the etiology, pathophysiology, complications, and comorbidities of T2DM and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns, the municipal registries, and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status. The present report includes data from 3451 participants, who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of 3 months. This study complies with the Declaration of Helsinki and has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare, and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent.

Figure 1 shows the flowchart of the study population. The main reasons for missing retina, skin, and plasma data were logistical (no equipment available, no trained researcher available, and technical failure). For longitudinal analyses, participants with prevalent depressive symptoms at baseline (n=134) and without available follow-up data (n=132) were excluded. The averaged follow-up period in this study population (n=2763) was 3.85 years (SD=1.00).

Materials and Methods

Assessment of MVD

All participants were asked to refrain from smoking and drinking caffeine-containing beverages 3 hours before the measurement.[15] A light meal (breakfast or lunch), low in fat content, was allowed at least 90 minutes before the examination. For retinal measurements, pupils were dilated with 0.5% tropicamide and 2.5% phenylephrine at least 15 minutes before the start of the examination. Skin blood flow measurements were performed in a climate-controlled room at 24°C.[15]

Retinal Arteriolar and Venular Dilation Responses

Retinal arteriolar and venular dilation to flicker light exposure was measured by the Dynamic Vessel Analyzer (Imedos, Jena, Germany), as previously described.[15] Briefly, a baseline recording of 50 seconds was followed by 40-second flicker light exposure followed by a 60-second recovery period. Baseline retinal and venular diameters were calculated as the average diameter size of the 20 to 50 seconds recording and were expressed in measurement units. Percentage dilation over baseline was based on the average dilation achieved at time points 10 and 40 seconds during the flicker stimulation period for both the arteriolar and venular response.

Skin Hyperemic Response

Heat-induced skin hyperemic response was measured by laser-Doppler flowmetry (Perimed, Järfälla, Sweden), as previously described.[15] Briefly, skin blood flow at the wrist, expressed in arbitrary perfusion units (PU), was recorded unheated for 2 minutes to serve as a baseline. After 2 minutes, the temperature of the laser-Doppler probe was rapidly and locally increased to 44°C and was kept constant until the end of the registration. The heat-induced skin hyperemic response was expressed as the percentage increase in average PU during the 23 minutes heating phase over the 2 minutes average baseline PU.

Plasma Biomarkers of ED

Since microvascular endothelium covers ≈98% of the total vascular surface area and synthetic capacity,[21] plasma biomarkers of ED can be regarded as reflecting mainly microvascular ED. sICAM-1 (soluble intercellular adhesion molecule-1), sVCAM-1 (soluble vascular adhesion molecule-1), and sE-selectin (soluble E-selectin) were measured at baseline in ethylenediaminetetraacetic acid (EDTA) plasma samples with commercially available 4-plex sandwich immunoassay kits with different standards and antibodies (Meso Scale Discovery [MSD], Rockville, MD). For this technique in this study, the intra- and inter-assay coefficients of variation were 10.3 and 8.4% for sICAM-1, 5.0 and 4.7% for sVCAM-1, and 2.9 and 7.4% for sE-selectin, respectively. vWF (Von Willebrand Factor) was quantified in citrate plasma using ELISA (Dako, Glostrup, Denmark). The intra- and inter-assay coefficients of variation were 3.0 and 4.3%, respectively. For reasons of statistical efficiency and to reduce the influence of the biological variability of each plasma marker, a standardized averaged sum score of ED was determined according to a predefined cluster of conceptually related biomarkers, as described elsewhere.[22]

Depression

Severity and presence of clinically relevant depressive symptoms (9-item Patient Health Questionnaire [PHQ-9]≥10) were assessed at baseline and during annual follow-up by a validated Dutch version of the PHQ-9.[23] The PHQ-9 is a self-administered questionnaire based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for a major depressive disorder as described previous. When 1 or 2 items were missing, the total-score was calculated as 9×(total points/9−number of missing items) and rounded to the nearest integer. A predefined cutoff score of ≥10 was used as a dichotomous scoring system for defining clinically relevant depressive symptoms.[24] PHQ-9 questionnaires were completed annually by participants during 4 years of follow-up. Incident depressive symptoms were defined as no depressive symptoms at baseline (PHQ-9 <10) and presence of clinically relevant depressive symptoms on at least one follow-up examination (PHQ-9≥10).

Major depressive disorder (MDD) was assessed at baseline by the Mini-International Neuropsychiatric Interview (MINI).[25] The MINI is a short diagnostic structured interview used to assess the presence of MDD in the preceding 2 weeks according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth

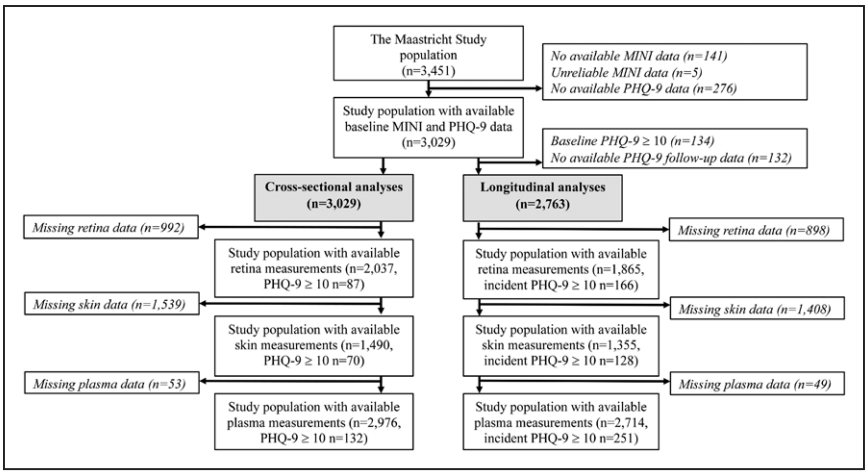

Figure 1. Flowchart of the study population. Missing data on retina and skin measurements were mainly due to logistic reasons (no equipment available, no trained researcher available, and technical failure). MINI indicates Mini-International Neuropsychiatric Interview; and PHQ-9, 9-item Patient Health Questionnaire.

Edition. We also used the MINI to assess lifetime history of MDD by asking about presence of symptoms during minimally 2 weeks in lifetime. The MINI was conducted at baseline only by trained staff members at the research center.

General Characteristics and Covariates

General characteristics and covariates were measured at baseline. Educational level (low, intermediate, high), partner status (partner/no partner), history of cardiovascular diseases, smoking status (never, current, former), alcohol consumption (none, low, high), and physical activity were assessed by questionnaires.[20] We measured, height, weight, waist circumference, office blood pressure, plasma glucose levels, hemoglobin A1c (HbA1c), plasma lipid profile, 24-hour urinary albumin excretion (twice), and plasma biomarkers of low-grade inflammation (LGI; high-sensitivity CRP [C-reactive protein], SAA [serum amyloid A], sICAM-1 [soluble intercellular adhesion molecule-1], IL-6 [interleukin-6], IL-8 [interleukin-8], and TNF-α [tumor necrosis factor alpha]) as described elsewhere.[20,22] sICAM-1 was included in both ED and LGI sum scores, as it is expressed by both monocytes and the endothelium.[26] T2DM status was defined by a standardized 2-hour 75-g oral glucose tolerance test after an overnight fast and use of antidiabetic medication as previously described.[20] Urinary albumin excretion was defined as normal (<15 mg/24 hour), micro- (15 to <30 mg/24 hour), and macroalbuminuria (≥30 mg/24 hour). Estimated glomerular filtration rate (eGFR; in mL/minute per 1.73 m^2) was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation based on both serum creatinine and serum cystatin C.[27] Medication use was assessed in a medication interview where generic name, dose, and frequency were registered.

Statistical Analysis

All statistical analyses were performed with Statistical Package for Social Sciences (version 25.0; IBM, Chicago, IL). General characteristics of the study population were presented as mean with SD or as percentages and were evaluated using ANOVA, Mann-Whitney *U* tests or $\chi 2$ tests, as appropriate. We inversed the flicker light-induced retinal arteriolar and venular dilation and heat-induced skin hyperemic responses (ie, multiplying it by −1) to reflect MVD.

PHQ-9 scores were right-skewed and contained many null values. To account for this, we used negative binomial regression analyses to assess the association of markers of MVD with prevalent depressive symptoms (PHQ-9 score). Logistic regression analyses were used to assess the associations of MVD with prevalent clinically relevant depressive symptoms (PHQ-9≥10) and MDD. Cox proportional regression analyses were used to assess the association of MVD with incident depressive symptoms (PHQ-9≥10), with time-in-study as time axis.

We adjusted for several covariates in the analyses. Model 1 was unadjusted. Model 2 was adjusted for age and sex, model 3 was additionally adjusted for T2DM because of the oversampling of T2DM in our study-population, and model 4 was additionally adjusted for systolic blood pressure, use of antihypertensive medication, body mass index, total-to-high-density lipoprotein cholesterol ratio, use of lipid-modifying medication, educational level, and smoking status. We also tested the interactions of the MVD markers with sex and T2DM on prevalent and incident depressive symptoms in the fully adjusted models. A 2-sided *P*-value <0.05 was considered statistically significant.

Results

General Characteristics of the Study Population

Table S1 in the Data Supplement shows the general characteristics of the study population at baseline with available retinal data, stratified for the prevalence and incidence of clinically relevant depressive symptoms. Participants had a mean age of 59.6±8.2 years and 49.4% were women. Participants with depressive symptoms had a worse cardiometabolic risk profile compared with participants without depressive symptoms (Table S1). The study populations on skin and plasma data were mainly comparable with regard to demographics, cardiovascular risk profile, medication use, and lifestyle profile (TableS S2 and S3). Participants with missing baseline PHQ-9 and MINI data (n=422) were statistically significant older, had a higher BMI and waist circumference, lower GFR levels, and higher levels of HbA1c, triglycerides, ED, and LGI than participants included in the analyses (data not shown).

Cross-Sectional Associations of MVD With Prevalent Depression

Results of the cross-sectional associations are shown in Table 1.

Retinal Arteriolar and Venular Dilation Response

A lower retinal arteriolar dilation response was not associated with more depressive symptoms (rate ratio per SD 1.05 [1.00–1.11]), clinically relevant depressive symptoms (odds ratio [OR] per SD 1.21 [0.97–1.52]), or MDD (OR 0.93 per SD [0.73–1.18]). A lower retinal venular dilation response was associated with more depressive symptoms (rate ratio per SD 1.05 [1.00–1.11]) and with clinically relevant depressive symptoms (OR per SD 1.42 [1.09–1.84]), after full adjustment, but not with MDD (OR 1.12 per SD [0.87–1.45]; Table 1). However, there was an interaction of retinal venular dilatation with sex

Table 1. Cross-Sectional Associations of Markers of Microvascular Dysfunction With Prevalent Depressive Symptoms and Major Depressive Disorder

Model	Depressive Symptoms (PHQ-9 score) Rate Ratio (95% CI)	*P*-Value	Clinically Relevant Depressive Symptoms (PHQ-9≥10) Odds Ratio (95% CI)	*P*-Value	Major Depressive Disorder (MINI) Odds Ratio (95% CI)	*P*-Value
Lower flicker light-induced retinal arteriolar dilation (per 1 SD)						
Model 1	1.05 (1.00–1.11)	0.063	1.21 (0.97–1.52)	0.097	0.93 (0.73–1.18)	0.556
Model 2	1.07 (1.02–1.13)	0.011	1.28 (1.01–1.63)	0.039	0.94 (0.73–1.19)	0.590
Model 3	1.05 (0.99–1.10)	0.089	1.22 (0.96–1.55)	0.105	0.89 (0.70–1.14)	0.360
Model 4*	1.04 (0.99–1.09)	0.168	1.13 (0.89–1.44)	0.327	0.87 (0.68–1.12)	0.270
Lower flicker light–induced retinal venular dilation (per 1 SD)						
Model 1	1.08 (1.02–1.14)	0.005	1.51 (1.18–1.93)	0.001	1.12 (0.87–1.45)	0.370
Model 2	1.08 (1.03–1.14)	0.002	1.57 (1.22–2.02)	<0.001	1.13 (0.87–1.46)	0.349
Model 3	1.07 (1.02–1.13)	0.006	1.51 (1.17–1.94)	0.001	1.10 (0.85–1.43)	0.454
Model 4*	1.05 (1.00–1.11)	0.049	1.42 (1.09–1.84)	0.009	1.10 (0.84–1.45)	0.482
Lower heat-induced skin hyperemic response (per 1 SD)						
Model 1	1.02 (0.96–1.09)	0.523	1.18 (0.90–1.54)	0.233	1.22 (0.89–1.66)	0.224
Model 2	1.10 (1.03–1.17)	0.004	1.37 (1.02–1.83)	0.034	1.28 (0.92–1.78)	0.137
Model 3	1.07 (1.01–1.14)	0.035	1.27 (0.95–1.71)	0.103	1.23 (0.89–1.71)	0.216
Model 4*	1.05 (0.99–1.12)	0.129	1.27 (0.93–1.75)	0.138	1.24 (0.87–1.76)	0.242
Higher ED score (per 1 SD)						
Model 1	1.09 (1.05–1.14)	<0.001	1.29 (1.11–1.49)	0.001	1.30 (1.10–1.54)	0.002
Model 2	1.15 (1.10–1.20)	<0.001	1.45 (1.25–1.67)	<0.001	1.35 (1.15–1.58)	<0.001
Model 3	1.11 (1.06–1.15)	<0.001	1.31 1.12–1.52)	0.001	1.25 (1.05–1.48)	0.011
Model 4*	1.06 (1.01–1.11)	0.013	1.16 (0.97–1.39)	0.106	1.11 (0.91–1.36)	0.317

n=2037 (retinal data), n=1490 (skin data), and n=2976 (plasma data). PHQ-9≥10 in n=87 (retinal data), n=70 (skin data), and n=132 (plasma data). MDD is present in n=66 (retinal data), n=53 (skin data), and n=98 (plasma data). Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: additionally adjusted for type 2 diabetes mellitus. Model 4: additionally adjusted for office systolic blood pressure, antihypertensive medication, total-to-HDL cholesterol ratio, lipid-modifying medication, body mass index, smoking status, and educational level. ED indicates endothelial dysfunction; MDD, major depressive disorder; MINI, mini-international neuropsychiatric interview; and PHQ-9, 9-item patient health questionnaire.

*Additional data on variables in model 4 were missing in n=54 (retinal data), n=47 (skin data), and n=76 (plasma data).

($P_{interaction}$=0.041) on clinically relevant depressive symptoms only. In stratified analyses, a lower venular dilatation was associated with clinically relevant depressive symptoms in women (OR 1.65 per SD [1.16–2.35]) but not in men (OR 1.12 per SD [0.74–1.68]). No interactions were found for T2DM.

Heat-Induced Skin Hyperemic Response

A lower heat-induced skin hyperemic response was associated with more depressive symptoms after adjustment for sex, age and T2DM (rate ratio 1.07 per SD [1.01–1.14]). This association was attenuated after adjustment for cardiovascular risk factors and educational level (rate ratio 1.05 per SD [0.99–1.12]). A lower heat-induced skin hyperemic response was also associated with clinically relevant depressive symptoms (OR, 1.37 per SD [1.02–1.83]), after adjustment for age and sex. After adjustment for T2DM, this association was attenuated (OR, 1.27 per SD [0.95–1.71]). No association was found between heat-induced skin hyperemic response and presence of MDD (OR, 1.22 per SD [0.89–1.66], Table 1). No interactions were found for sex or T2DM.

Plasma Biomarkers of Microvascular Endothelial Dysfunction

A higher ED score was associated with more depressive symptoms (rate ratio, 1.06 per SD [1.01–1.11]), after full adjustment. In addition, a higher ED score was associated with clinically relevant depressive symptoms and MDD after adjustment for age, sex, and T2DM (OR, 1.31 per SD [1.12–1.52], and OR, 1.25 per SD [1.05–1.48]). These associations were attenuated after adjustment for cardiovascular risk factors and educational level (OR, 1.16 per SD [0.97–1.39] and OR, 1.11 per SD [0.91–1.36], Table 1). Associations of the individual markers of ED were similar in direction and consistent with the associations of the ED score (data not shown). No interactions were found for sex or T2DM.

Longitudinal Associations of MVD With Incident Depressive Symptoms

A lower flicker light–induced retinal arteriolar dilation at baseline was associated with an increased risk of incident depressive symptoms after full adjustment (hazard ratio [HR],

1.23 per SD [1.04–1.46]; Table 2). Flicker light–induced retinal venular dilatation at baseline was not associated with incident depressive symptoms (HR, 1.10 per SD [0.94–1.29]). A lower heat-induced skin hyperemic response at baseline was not associated with incident depressive symptoms after adjustment for age and sex (HR, 1.20 per SD [0.98–1.46]). A higher ED score at baseline was associated with an increased risk for incident depressive symptoms after full adjustment (HR, 1.19 per SD [1.05–1.35]; Table 2). Associations with the individual markers of ED were similar in direction and consistent with the associations of the ED score (data not shown). No interactions were found for sex or T2DM.

Additional Analyses

Results of additional analyses are shown in the Data Supplement. Qualitatively similar associations were found after (1) replacing office systolic blood pressure with 24-hour ambulatory systolic blood pressure, and BMI with waist circumference (Tables S4 and S8), (2) additional adjustment for use of antidepressant medication (prescribed for depression or neuropathy), antipsychotic and anxiolytic medication, antidiabetic and insulin medication, history of cardiovascular disease, LGI, physical activity, alcohol use, or cognitive functioning (Tables S5 and S9), (3) excluding participants with MDD at baseline for the longitudinal analyses (Table S11) using absolute values instead of percentages for the retina and skin analyses (Tables S6 and S10), and (5) using a control group with only one or no missing follow-up measurements for the incidence analyses (data not shown). The associations between markers of MVD and incident depressive symptoms became slightly stronger after excluding participants with an age of MDD onset of ≤40 years (Table S12), the cross-sectional association between a lower retinal venular dilatation and prevalent depressive symptoms attenuated although other cross-sectional analyses did not materially change the results (Table S7). Overall MVD, calculated as the standardized average of all MVD markers, resulted in a substantive smaller study population (≈35% of the original) but stronger associations (Table S13).

Table 2. Longitudinal Associations of Markers of Microvascular Dysfunction With Incident Depressive Symptoms

Model	Incident Clinically Relevant Depressive Symptoms (PHQ-9≥10) Hazard Ratio (95% CI)	*P*-Value
Lower flicker light-induced retinal arteriolar dilation (per 1 SD)		
Model 1	1.28 (1.09–1.51)	0.003
Model 2	1.29 (1.09–1.52)	0.003
Model 3	1.23 (1.05–1.46)	0.013
Model 4*	1.23 (1.04–1.46)	0.018
Lower flicker light–induced retinal venular dilation (per 1 SD)		
Model 1	1.10 (0.94–1.29)	0.238
Model 2	1.10 (0.94–1.28)	0.251
Model 3	1.07 (0.91–1.25)	0.414
Model 4*	1.05 (0.89–1.23)	0.567
Lower heat-induced skin hyperemic response (per 1 SD)		
Model 1	1.22 (1.00–1.48)	0.046
Model 2	1.20 (0.98–1.46)	0.076
Model 3	1.16 (0.95–1.42)	0.146
Model 4*	1.17 (0.96–1.43)	0.130
Higher ED score (per 1 SD)		
Model 1	1.35 (1.21–1.51)	<0.001
Model 2	1.37 (1.22–1.53)	<0.001
Model 3	1.26 (1.12–1.41)	<0.001
Model 4*	1.19 (1.05–1.35)	0.008

n=1865 (retina data), n=1355 (skin data), and n=2714 (plasma data). Incident depressive symptoms in n=166 (retinal data), n=128 (skin data), and n=251 (plasma data). Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: additionally adjusted for type 2 diabetes mellitus. Model 4: additionally adjusted for office systolic blood pressure, antihypertensive medication, total-to-HDL cholesterol ratio, lipid-modifying medication, body mass index, smoking status and educational level. ED indicates endothelial dysfunction; and PHQ-9, 9-item patient health questionnaire.

*Additional data on variables in model 4 were missing in n=45(retinal data), n=41(skin data), and n=64 (plasma data).

Discussion

This population-based study demonstrates that functional markers of the microcirculation in the retina and plasma are associated with prevalent and incident depressive symptoms, independently of demographic, cardiovascular, and lifestyle risk factors. These markers of MVD may represent early deficits in the microcirculation because any functional impairments found in our study are likely to precede structural impairments, supporting the concept that early MVD plays a role in the pathophysiology of LLD. However, no association was found between the skin hyperemic response and prevalent or incident depressive symptoms after full adjustment, nor between any marker of MVD with prevalent MDD.

Our results are in line with previous studies on plasma markers of ED,[16,22] and retinal diameters in individuals with T2DM,[28] and provide additional evidence for the association of attenuated microvascular reactivity in the retina in individuals with depression in the general population. However, differences were found between the retinal arteriolar and venular microvascular reactivity. A lower retinal arteriolar response at baseline was associated only with a higher incidence of depressive symptoms. A lower retinal venular response at baseline was associated only with a higher prevalence of depressive symptoms at baseline in women, not in men. These differences may have been a result of underlying pathophysiological differences. Central retinal arteriolar diameters and central retinal venular diameters have been associated with different risk factors. A smaller central retinal arteriolar diameter has been associated with current alcohol consumption, blood pressure, and body mass index, although a larger CRVE has additionally been associated with serum HDL cholesterol, smoking, diabetes mellitus, and inflammation markers,[29] suggesting different effects of these risk factors on arterioles and venules. Although we measured arteriolar and venular reactivity instead of diameters, similar differences in effects

may have contributed to the observed differences in the associations between retinal arteriolar and venular reactivity and depression. The associations between the skin hyperemic response and depressive symptoms became nonsignificant after adjustment for cardiovascular risk factors. The absence of this association could be because of lack of power because the study population with skin data comprised only half the number of participants of the plasma marker study population. Alternatively, the association between the skin hyperemic response and depressive symptoms may be mediated by cardiovascular risk factors. Cardiovascular risk factors might be on the causal path and our final models may thus be overadjusted. For example, T2DM and hypertension are associated with both MVD and depression,[30,31] adjustment for these variables may lead to overadjustment since part of the variance between MVD and depression is explained by these variables. Furthermore, different mechanisms may be involved in skin hyperemic response as compared with dilatation in both the retinal arterioles and venules.

Several pathophysiological mechanisms may be involved in the association of MVD with LLD.[10] First, arterioles are responsible for distributing blood according to metabolic demand.[32] ED of vessels supplying the brain may contribute to disruption of the normal distribution of blood and induce chronic ischemia. Second, tight junctions of the cerebral endothelial cells constitute the blood-brain barrier.[32] Loss of normal endothelial function may contribute to blood-brain barrier disruption and to leakage of blood cells and/or fluid, which causes disruption of the normal architecture, including damaged arteriolar smooth muscle cells and fibrin depositions.[10] Third, venules collect capillary blood and play a role in determining capillary pressure.[30] ED and blood-brain barrier disruption may lead to venular wall collagenosis and thickening, which may obstruct blood flow and impair the perivascular drainage through the brain, contributing to cerebral ischemia.[33] Fourth, ED impairs neurovascular coupling, the mechanism responsible for regulation of the blood flow to different parts of the brain in according to the metabolic demand.[34]

Strengths of our study include its large sample size and population-based longitudinal design; the annual assessment of the PHQ-9 to assess depressive symptoms over a 4-year period; the use of the MINI to assess MDD at baseline; the comparable incidence rate of depression to other population-based studies; the extensive assessment of potential confounders used in main and additional analyses; and the use of multiple direct measures of specific MVD. All markers of MVD included in the present study are likely to reflect MVD, probably in conjunction with vascular smooth muscle cell dysfunction and/or neuronal dysfunction.[35–37] Impairments in both flicker light–induced retinal dilation and heat-induced skin hyperemia have been shown to be partly nitric oxide-dependent.[38,39] Plasma biomarkers of ED also reflect microvascular endothelial function because ≈98% of the endothelium is located in the microcirculation.[21]

This study has some limitations. First, there could have been selection and/or attrition bias, which is inherent to prospective population-based studies; individuals with more severe depressive symptoms or with greater comorbidity may have been more likely not to participate or to withdraw. Although the dropout rate was relatively low, this may have led to an underestimation of the observed findings. Second, the study population was well treated with regard to cardiovascular risk factors, which may have led to less variations in MVD. As a result, the effects of MVD in this study may have been suppressed and associations may be stronger in individuals with more severe MVD. In addition, the population was mainly of white ethnicity; heterogeneous with respect to their histories of depression; and aged 40 to 75 years, which should be considered when extrapolating these findings to other populations. Finally, longitudinal data only included depressive symptoms as measured with the PHQ-9 questionnaire. The PHQ-9 questionnaire is a screening instrument to measure depressive symptoms that consists of the criteria upon which MDD is based.[23] High scores on the PHQ-9 are suggestive for depressive symptoms but do not necessarily equate with MDD.

In conclusion, we show that markers of early MVD in the retina and plasma are associated with prevalent and incident depressive symptoms in the general population, independently of major demographic, cardiovascular, and lifestyle risk factors.

Perspectives

These findings support the concept that early generalized MVD is associated with the development of LLD and may play a role in its pathophysiology. MVD might, therefore, be a target for prevention strategies and treatment of LLD. Evidence suggests that lifestyle modifications, such as weight loss and exercise, may, at least in part, favorably influence MVD.[40] In addition, drugs, such as renin-angiotensin-aldosterone system inhibitors and antihyperglycemic agents (ie, metformin and GLP-1R [glucagon-like peptide 1 receptor] agonists), may improve microvascular function, possibly beyond their blood pressure- or glucose-lowering effects.[41] Other longitudinal population-based studies are needed to replicate these findings.

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Disclosures

None.

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Novelty and Significance

What Is New?

- We tested for the first time the association between both direct and indirect markers of microvascular dysfunction with prevalent and incident depressive symptoms in a large population-based cohort.
- Microvascular dysfunction was measured by novel techniques; flicker light–induced retinal arteriolar and venular dilation, skin hyperemia, and plasma biomarkers of endothelial dysfunction. Depression was assessed at baseline and annually over 4 years of follow-up.

What Is Relevant?

- We found an association of retinal venular dilatation and plasma markers of endothelial dysfunction with prevalent depressive symptoms.
- Retinal arteriolar dilatation and plasma markers of endothelial dysfunction were associated with incident depressive symptoms.
- Skin hyperemia was not associated with prevalent or incident depressive symptoms.

Summary

- Our findings support the hypothesis that early generalized microvascular dysfunction is associated with the development of late-life depression and may play a role in its pathophysiology.
- Microvascular dysfunction may be a target for prevention strategies of late-life depression.
- Future longitudinal studies are needed to further evaluate the association of microvascular dysfunction and late-life depression.